The importance of being earnest…

…or at least active…

Activity influences:

1. Growth/aging of muscle, NMJ and synaptic strength
2. Synapse elimination: the NMJ as a 'Hebbian' synapse
3. Synaptic degeneration
http://myathleticlife.com/2012/01/sarcopenia-doomed-age-related-muscle-loss/

40 year old triathlete

74 year old sedentary male

http://miloahs.lib.uci.edu/2012/03/09/sarcopenia-doomed-age-related-muscle-loss
Exercise confers little benefit on sarcopenia

![Graph showing age-related changes in sarcopenia.](image)


Monoinnervated NMJ's are stable and grow throughout life

![Images of monoinnervated NMJ's.](image)


Quantal Content (variance method) at NMJ of rat HD

![Graph showing Quantal Content.](image)

(Based on Kelly & Roberts, 1977 and Kelly, 1978)
Impaired neurotransmitter release

Increased sensitivity retargets set point muscle excitation

Set point muscle excitation

Upregulation of quantal content in α-BTX treated rats


Li, TI & Thompson, WJ (2011) J Neurosci 31:14910–14919
Paralysis (neuromuscular block) promotes sprouting

Duchen, 1970

Exercise modestly increases endplate size and quantal content


So, activity may have a biphasic effect...
Denervation changes muscle phenotype

Most of these properties are reversed, restoring the innervated phenotype, by direct electrical stimulation.

Conclusion:
Activity (exercise), nutrition and aging have clear effects on metabolism and muscle growth; but the effects are complex.

Based on D. Purves & J.W. Lichtman, Principles of Neural Development.
Activity influences:

1. Growth/aging of muscle, NMJ and synaptic strength
2. Synapse elimination: the NMJ as a 'Hebbian' synapse
3. Synaptic degeneration

"When an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency as one of the cells firing B is increased."


In 1949 D.O. Hebb (1) formulated his "neuropsychological postulate" of learning which states: "When an axon of cell A is near enough to another cell B to exert a physiological influence on it, and repeatedly and persistently takes part in firing it, some growth process or change takes place in one or both cells such that A's efficiency as one of the cells firing B is increased."

Paraphrasing…
“Cells that fire together, wire together”
“Use it or lose it”

“We observe that A is more effective in exciting cell B and consistently interconnects by repeating and persistently firing part of B. Some growth processes or metabolic changes take place in one or both cells such that A’s efficacy as one of the cells firing B is increased.”

“When the presynaptic axon of cell A repeatedly and persistently fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A’s efficacy is decreased.”
G.S. Stent (1972) PNAS 70, 997-1001

Motor terminals compete for synaptic occupancy during synapse elimination

Synapse elimination is influenced by activity

![Graph showing synapse elimination over age (days)]

Rodent 4th Deep Lumbrical Muscles (4DL) provide opportunities to explore activity-dependent plasticity of NMJ

![Diagram of rodent 4DL muscles]

Betz & Ridge, 1984

Selective stimulation biases synapse elimination

![Diagram showing selective stimulation effects on synapse elimination]

MPN, LPN, SN

MPN LPN SN

4DL

Stim

Control

Unstimulated

Betz & Ridge, 1984
Active motor units have a competitive advantage over inactive units

Is activity sufficient for synapse elimination?
Is activity necessary for synapse elimination?

Replacing asynchronous activity with synchronous activity...
leads to a greater level of polyneuronal innervation

Conclusion:

Activity is influential, but not decisive in determining the fate of neuromuscular synapses

Activity influences:

1. Growth/aging of muscle, NMJ and synaptic strength
2. Synapse elimination: the NMJ as a ‘Hebbian’ synapse
3. Synaptic degeneration
Synaptic degeneration precedes axonal degeneration in Wld\(S\) mice

Synapses degenerate in Wld\(S\) homozygotes over 3-10 days

(YFP does not interfere with the Wld\(S\) phenotype)
Effects of stimulation on synaptic degeneration in vitro

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Does activity influence (prime or protect) synaptic degeneration in WldS mice?

2-3 weeks of voluntary wheel running does not delay synaptic degeneration in heterozygous WldS mice

Rosalind Brown
Electrophysiological analysis of the number of responsive fibres in the Flexor Digitorum Brevis muscle

Inactivity inhibits the WldS phenotype: Physiology

- Morphological analysis of the number of responsive fibres in the Flexor Digitorum Brevis muscle.

Inactivity inhibits the WldS phenotype: Morphology

- YFP16-WldS mice; Tritc-α-BTX staining
- Number of occupied endplates counted

Conclusion

Inactivity sensitises neuromuscular junctions to triggers of synaptic degeneration in WldS mice.
Motor neurone disease (e.g., ALS)

Hypertrophy and Atrophy in ALS

Grouping of Slow (Type I) and Fast MHC (Type II) muscle fibres in ALS
Activity mitigates onset but not progression of ALS in female SOD1 mice
Or is it males...

Swimming is better than running, ?

Preterminal axons atrophy, then fragment, before motor nerve terminals

(Wheel running does not influence this process)
Summary

- Activity (exercise), nutrition and aging have clear effects on metabolism and muscle growth; but the effects are complex.
- Activity is influential, but not decisive in determining the fate of neuromuscular synapses.
- Inactivity sensitises neuromuscular junctions to triggers of synaptic degeneration in Wld<sup>S</sup> mice.
- "Exercise regimes [may] merit more detailed clinical evaluation in ALS."